NDA 20-45l/S-006

JUL —6 2000

Axcan Scandipharm Inc.
22 Inverness Parkway
Birmingham, Alabama 35242

Attention: Francois Martin, M.D. Vice President, Scientific Affairs

Dear Dr. Martin:

Please refer to your supplemental new drug application dated May 18, 2000, received May 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Photofrin (porfirner sodium) for Injection.

This "Changes Being Effected" supplemental new drug application provides for previously unreported adverse events.

We note the June 22,2000 agreement to add "Conventional" to the following bolded sentence in PRECAUTIONS Photosensitivity.

> "Conventional UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light."

We also note your June 29, 2000 agreement to modify "burning sensations" to "burning sensation" in ADVERSE REACTIONS.

We have completed the review of this supplemental application and have concluded that, with the modification noted above, adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted May 18, 2000 labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted May 18, 2000 labeling text with the modification noted above.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-451/S-006." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul Zimmerman, Project Manager, at (301) 594-5775.

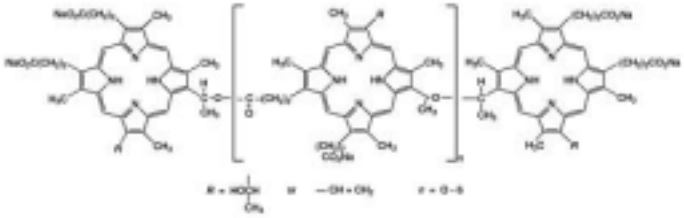
Sincerely yours,

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

PHOTOFRIN® (porfimer sodium) for Injection

DESCRIPTION

PHOTOFRIN® (porfimer sodium) for Injection is a photosensitizing agent used in the photodynamic therapy (PDT) of tumors. Following reconstitution of the freeze-dried product with 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), it is injected intravenously. This is followed 40-50 hours later by illumination of the tumor with laser light (630 nm wavelength). PHOTOFRIN® is not a single chemical entity; it is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units. It is a dark red to reddish brown cake or powder. Each vial of PHOTOFRIN® contains 75 mg of porfimer sodium as a sterile freeze-dried cake or powder. Hydrochloric Acid



and/or Sodium Hydroxide may be added during manufacture to adjust pH. There are no preservatives or other additives. The structural formula below is representative of the components present in PHOTOFRIN®.

CLINICAL PHARMACOLOGY

Pharmacology

The cytotoxic and antitumor actions of PHOTOFRIN® are light and oxygen dependent. Photodynamic therapy (PDT) with PHOTOFRIN® is a two-stage process. The first stage is the intravenous injection of PHOTOFRIN®. Clearance from a variety of tissues occurs over 40-72 hours, but tumors, skin, and organs of the reticuloendothelial system (including liver and spleen) retain PHOTOFRIN® for a longer period. Illumination with 630 nm wavelength laser light constitutes the second stage of therapy. Tumor selectivity in treatment occurs through a combination of selective retention of PHOTOFRIN® and selective delivery of light. Cellular damage caused by PHOTOFRIN® PDT is a consequence of the propagation of radical reactions. Radical initiation may occur after PHOTOFRIN® absorbs light to form a porphyrin excited state. Spin transfer from PHOTOFRIN® to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals. Tumor death also occurs through ischemic necrosis secondary to vascular occlusion that appears to be partly mediated by thromboxane A_2 release. The laser treatment induces a photochemical, not a thermal, effect. The necrotic reaction and associated inflammatory responses may evolve over several days.

Pharmacokinetics

Following a 2 mg/kg dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was 15 ± 3 mcg/mL, the elimination half-life was 250 ± 285 hours, the steady-state volume of distribution was 0.49 ± 0.28 L/kg, and the total plasma clearance as 0.051 ± 0.035 mL/min/kg. The mean plasma concentration at 48 hours was 2.6 ± 0.4 mcg/mL. The influence of impaired hepatic function on PHOTOFRIN® disposition has not been evaluated.

PHOTOFRIN® was approximately 90% protein bound in human serum, studied in vitro. The binding was independent of concentration over the concentration range of 20-100 mcg/mL.

Clinical Studies

Clinical studies of PDT with PHOTOFRIN® were conducted in patients with obstructing esophageal and endobronchial nonsmall cell lung cancers and in patients with early-stage radiologically occult endobronchial cancer. In all clinical studies, the method of PDT administration was essentially identical. A course of therapy consisted of one injection of PHOTOFRIN® (2 mg/kg administered as a slow intravenous injection over 3-5 minutes) followed by up to two nonthermal applications of 630 nm laser light. Doses of 300 J/cm of tumor length were used in esophageal cancer. Doses of 200 J/cm were used in endobronchial cancer for both palliation of obstructing cancer and treatment of superficial lesions. The first application of light occurred 40-50 hours after injection. Debridement of residua was performed via endoscopy/bronchoscopy 96-120 hours after injection, after which any residual tumor could be retreated with a second laser light application at the same dose used for the initial treatment. Additional courses of PDT with PHOTOFRIN® were allowed after 1 month, up to a maximum of three courses.

Esophageal Cancer

PDT with PHOTOFRIN® was utilized in a multicenter, single-arm study in 17 patients with completely obstructing esophageal carcinoma. Assessments were made at 1 week and 1 month after the last treatment procedure. As shown in Table 1, after a single course of therapy, 94% of patients obtained an objective tumor response and 76% of patients experienced some palliation of their dysphagia. On average, before treatment these patients had difficulty swallowing liquids, even saliva. After one course of therapy, there was a statistically significant improvement in mean dysphagia grade (1.5 units, $p < 0.05$) and 13 of 17 patients could swallow liquids without difficulty 1 week and/or 1 month after treatment. Based on all courses, three patients achieved a complete tumor response (CR). In two of these patients, the CR was documented only at Week 1 as they had no further assessments. The third patient achieved a CR after a second course of therapy, which was supported by negative histopathology and maintained for the entire follow-up of 6 months.

Of the 17 treated patients, 11 (65%) received clinically important benefit from PDT. Clinically important benefit was defined hierarchically as a complete tumor response (3 patients), achievement of normal swallowing (2 patients went from Grade 5 dysphagia

to Grade 1), or achievement of a marked improvement of two or more grades of dysphagia with minimal adverse reactions (6 patients). The median duration of benefit in these patients was 69+ days. Duration of benefit was calculated only for the period with documented evidence of improvement. All of these patients were still in response at their last assessment and, therefore, the estimate of 69 days is conservative. The median survival for these 11 patients was 115 days.

TABLE 1. Course 1 Efficacy Results in Patients with Completely Obstructing Esophageal Cancer

EFFICACY PARAMETER	PDT n=17
OBJECTIVE TUMOR RESPONSE [a]	
Week 1	82%
Month 1	35% [b]
Any assessment [c]	94%
IMPROVEMENT [d] IN DYSPHAGIA	
Week 1	71%
Month 1	47%
Any assessment [c]	76%
MEAN DYSPHAGIA GRADE [e] AT BASELINE	4.6
MEAN IMPROVEMENT [e] IN DYSPHAGIA GRADE (units)	
Week 1	1.4
Month 1	1.5
MEAN NUMBER OF LASER APPLICATIONS	1.4

a CP+PR, CR = complete response (absence of endoscopically visible tumor), PR = partial response (appearance of a visible lumen)

b Eight of the 17 treated patients did not have assessments at Month 1.

c Week 1 or Month 1

d Patients with at least a one-grade improvement in dysphagia grade

e Dysphagia Scale: Grade 1 = normal swallowing, Grade 2 = difficulty swallowing some hard solids; can swallow semisolids, Grade 3 = unable to swallow any solids; can swallow liquids, Grade 4 = difficulty swallowing liquids, Grade 5 = unable to swallow saliva.

Endobronchial Cancer

Two randomized multicenter Phase 3 studies were conducted to compare the safety and efficacy of PHOTOFRIN® PDT versus Nd:YAG laser therapy for reduction of obstruction and palliation of symptomatic patients with partially or completely obstructing endobronchial nonsmall cell lung cancer. Assessments were made at 1 week and at monthly intervals after treatment. Table 2 shows the results from all randomized patients in the two studies combined. Objective tumor response rates (CR + PR), which demonstrate reduction of obstruction, were 59% for PDT and 58% for Nd:YAG at Week 1. The response rate at 1 month or later was 60% for PDT and 41% for Nd:YAG.

TABLE 2. Efficacy Results from Studies in Late-stage Obstructing Endobronchial Cancer-All Randomized Patients [a]

EFFICACY PARAMETER (% of Patients)	PDT n=102	Nd:YAG n=109
OBJECTIVE TUMOR RESPONSE [b]		
Week 1	59%	58%
Month 1 or later	60%	41%a
ATELECTASIS IMPROVEMENT [c]	n = 60	n = 71
Week 1	35%	18%
Month 1 or later	35%	20%

a Statistical comparisons were precluded by the amount of missing data at Month 1 or later (e.g. for tumor response, PDT 28% missing, Nd:YAG 38%).

b CR+PR, CR = complete response (absence of bronchoscopically visible tumor), PR = partial response (increase of $\geq$ 50% in the smallest luminal diameter); for completely obstructing tumors, any appearance of a lumen).

c In patients with atelectasis at baseline

Patient symptoms were evaluated using a 5- or 6-grade pulmonary symptom severity rating scale for dyspnea, cough, and hemoptysis. Patients with moderate to severe symptoms are those most in need of palliation. Improvements of 2 or more grades are considered to be clinically significant. Table 3 shows the percentages of patients with moderate to severe symptoms at baseline who demonstrated a 2-grade improvement at any time during the interval evaluated.

TABLE 3. Efficacy Results from Studies in Late-stage Obstructing Endobronchial Cancer-Clinically Significant Improvements in Patients with Moderate to Severe Symptoms at Baseline

CLINICALLY SIGNIFICANT SYMPTOM IMPROVEMENT (% of Patients)	PDT	Nd:YAG
ANY SYMPTOM	n=89	n=89
Week 1	25%	29%
Month 1 or later	40%	27% [a]
DYSPNEA	n=60	n=68
Week 1	15%	18%
Month 1 or later	23%	13%
COUGH	n=63	n=65
Week 1	6%	9%
Month 1 or later	24%	8%
HEMOPTYSIS	n=24	n=31
Week 1	58%	29%
Month 1 or later	79%	35%

a Statistical comparisons were precluded by the amount of missing data at Month 1 or later.

b Dyspnea was graded on a 6-point severity rating scale; cough and hemoptysis on 5-point scales. Clinically significant improvement was defined as a change of at least two grades from baseline.

In a separate retrospective analysis, patients were individually evaluated to identify those patients whose benefit to risk ratio was most favorable, i.e., those who obtained clinically important benefit with minimal adverse reactions. Clinically important benefit was defined as one of the following:

1. a substantial improvement in pulmonary symptoms at Month 1 or later (dyspnea $\geq$2 grades, hemoptysis $\geq$3 grades, cough $\geq$3 grades or increase in $FEV_1 \geq 40\%$);
2. a moderate improvement in symptoms at Month 2 or later (dyspnea 1 grade, cough 2 grades, hemoptysis 2 grades or increase in $FEV_1 \geq 20\%$); or
3. a durable objective tumor response (CR or PR maintained to Month 2 or longer).

Thirty-six (36) of the 99 PDT-treated patients (36%) and 23 of the 99 Nd:YAG-treated patients (23%) received clinically important benefit with only minimal or moderate toxicities of short duration. 34 of 99 PDT-treated patients demonstrated improvements in 2 or more efficacy endpoints (dyspnea, cough, hemoptysis, sputum, atelectasis, pulmonary function tests of FEV_1 or FVC, Karnofsky Performance Score or tumor response) and 29 patients had improvements in 3 or more. The median duration of documented benefit in the 36 patients was 63 days. In these patients with late-stage obstructing lung cancer, median survival was 174 days in PDT-treated patients and 161 days in Nd:YAG-treated patients.

The efficacy of PHOTOFRIN® PDT was also evaluated in the treatment of microinvasive endobronchial tumors in 62 inoperable patients in three noncomparative studies. Microinvasive lung cancer is defined histologically as disease which invades beyond the basement membrane but not through or into the cartilage. For 11 of the 62 patients, it was clearly documented that surgery and radiotherapy were not indicated. These 11 patients were all inoperable for medical or technical reasons. Radiotherapy was not indicated due to prior high-dose radiotherapy (7 patients), poor pulmonary function (2 patients), multifocal mutilobar disease (1 patient), and poor medical condition (1 patient). As shown in Table 4, the complete tumor response rate, biopsy-proven at least 3 months after treatment, was 50%, median time to tumor recurrence was more than 2.7 years, median survival was 2.9 years and disease-specific survival was 4.1 years.

TABLE 4. Overall Efficacy Results in Patients with Superficial Endobronchial Tumors

EFFICACY PARAMETER	PDT	
	n=11	n=62
COMPLETE TUMOR RESPONSE, BIOPSY-PROVEN AT 3 MONTHS		
Number of Patients (%)	3 (27%)	31 (50%) [a]
TIME TO TUMOR RECURRENCE IN PATIENTS WITH COMPLETE RESPONSE		
Number of Patients (%) with Recurrences	1 (33%)	11 (35%)
Median Time to Tumor Recurrence		>2.7 years
[95% Confidence Interval]		[1.6,-- [b]]
SURVIVAL		
Number of Patients (%) who Died of Any Cause	4 (36%)	32 (52%)
Median Survival		2.9 years
[95% Confidence Interval]		[2.1, 5.7]
DISEASE-SPECIFIC SURVIVAL		
Number of Patients (%) who Died of Lung Cancer	3 (27%)	22 (35%)
Median Disease-Specific Survival		4.1 years
[95% Confidence Interval]		[2.5,-- [b]]

a Not included are an additional 18 patients (6 patients not eligible for surgery or radiotherapy) who had complete tumor responses which were documented earlier than 3 months after treatment.

b The upper limit of the confidence interval could not be estimated due to an insufficient number of patients whose tumors recurred (Time to Tumor Recurrence) or who died (Survival).

INDICATIONS AND USAGE

Photodynamic therapy with PHOTOFRIN® is indicated for:

- palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.
- reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC).
- treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated.

CONTRAINDICATIONS

PHOTOFRIN® is contraindicated in patients with porphyria or in patients with known allergies to porphyrins.

PDT is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula.

PDT is contraindicated in patients with tumors eroding into a major blood vessel.

WARNINGS

Following injection with PHOTOFRIN® precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light (see PRECAUTIONS , General Precautions and Information for Patients).

Esophageal Cancer

If the esophageal tumor is eroding into the trachea or bronchial tree, the likelihood of tracheoesophageal or bronchoesophageal fistula resulting from treatment is sufficiently high that PDT is not recommended.

Patients with esophageal varices should be treated with extreme caution. Light should not be given directly to the variceal area because of the high risk of bleeding.

Endobronchial Cancer

Patients should be assessed for the possibility that a tumor may be eroding into a pulmonary blood vessel (see CONTRAINDICATIONS). Patients at high risk for fatal hemoptysis include those with large, centrally located tumors, those with cavitating tumors or those with extensive tumor extrinsic to the bronchus.

If the endobronchial tumor invades deeply into the bronchial wall, the possibility exists for fistula formation upon resolution of tumor.

PDT should be used with extreme caution for endobronchial tumors in locations where treatment-induced inflammation could obstruct the main airway, e.g., long or circumferential tumors of the trachea, tumors of the carina that involve both mainstem bronchi circumferentially, or circumferential tumors in the mainstem bronchus in patients with prior pneumonectomy.

PRECAUTIONS

General Precautions and Information for Patients

<u>Photosensitivity</u>

All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, etc.) for 30 days. The photosensitivity is due to residual drug which will be present in all parts of the skin. Exposure of the skin to ambient indoor light is, however, beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, patients should not stay in a darkened room during this period and should be encouraged to expose their skin the ambient indoor light. The level of photosensitivity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurs within 24 hours, the

patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue precautions for another 2 weeks before retesting. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. **UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.**

Ocular Sensitivity

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in patients who received PHOTOFRIN®. For 30 days, when outdoors, patients should wear dark sunglasses which have an average white light transmittance of <4%.

Use Before or After Radiotherapy

If PDT is to be used before or after radiotherapy, sufficient time should be allotted between the two therapies to ensure that the inflammatory response produced by the first treatment has subsided before commencing the second treatment. The inflammatory response from PDT will depend on tumor size and extent of surrounding normal tissue that receives light. It is recommended that 2 to 4 weeks be allowed after PDT before commencing radiotherapy. Similarly, if PDT is to be given after radiotherapy, the acute inflammatory reaction from radiotherapy usually subsides within 4 weeks after completing radiotherapy, after which PDT may be given.

Chest Pain

As a result of PDT treatment, patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Respiratory Distress

Patients with endobronchial lesions must be closely monitored between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress. Inflammation, mucositis, and necrotic debris may cause obstruction of the airway. If respiratory distress occurs, the physician should be prepared to carry out immediate bronchoscopy to remove secretions and debris to open the airway.

Avoidance of Pregnancy

Women of childbearing potential should practice an effective method of contraception during therapy (see Pregnancy).

Drug Interactions

There have been no formal interaction studies of PHOTOFRIN® and any other drugs. However, it is possible that concomitant use of other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemia agents, thiazide diuretics, and griseofulvin) could increase the photosensitivity reaction.

PHOTOFRIN® PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many drugs could influence the effects of PDT, possible examples of which are described below. There are no human data that support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sufloxide, b-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN® PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decrease the efficacy of the treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN®. In vitro, PHOTOFRIN® PDT did not cause mutations in the Ames test, nor did it cause chromosome aberrations or mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. PHOTOFRIN® caused <2-fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3-fold increase in Chinese hamster lung fibroblasts irradiated with near UV light. PHOTOFRIN® PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. PHOTOFRIN® PDT caused a light-dose dependant increase in DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. The mutagenicity of PHOTOFRIN® without light has not been adequately determined. In vivo, PHOTOFRIN® did not cause chromosomal aberrations in the mouse micronucleus test.

PHOTOFRIN® given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through Day 7 of pregnancy caused no impairment of fertility. In this study, long-term dosing with PHOTOFRIN® caused discoloration of testes and ovaries and hypertrophy of the testes. PHOTOFRIN® also caused decreased body weight in the parent rats.

Pregnancy: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. PHOTOFRIN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PHOTOFRIN® given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m ^{2} basis) for 10 days caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight. PHOTOFRIN® caused no major malformations when given to rabbits intravenously during organogenesis at 4 mg/kg/d (0.65 times the clinical dose on a mg/m ^{2} basis) for 13 days. This dose caused maternal toxicity resulting in increased resorptions, decreased litter size, and reduced fetal body weight.

PHOTOFRIN® given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m ^{2} basis) for at least 42 days caused a reversible decrease in growth of offspring. Parturition was unaffected.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PHOTOFRIN®, women receiving PHOTOFRIN® must not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Approximately 70% of the patients treated with PDT using PHOTOFRIN® in clinical trials were over 60 years of age. There was no apparent difference in effectiveness or safety in these patients compared to younger people. Dose modification based upon age is not required.

ADVERSE REACTIONS

Systemically induced effects associated with PDT with PHOTOFRIN® consist of photosensitivity and mild constipation. All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid sunlight and bright indoor light (see PRECAUTIONS). Photosensitivity reactions occurred in approximately 20% of patients treated with PHOTOFRIN® in clinical studies. Typically these reactions were mostly mild to moderate erythema but they also included swelling, itching, burning sensations, feeling hot, or blisters. In a single study of 24 healthy subjects, some evidence of photosensitivity reactions occurred in all subjects. Other less common skin manifestations were also reported in areas where sensitivity reactions had occurred, such as increased hair growth, skin discoloration, skin nodules, increased wrinkles and increased skin fragility. These manifestations may be attributable to a pseudoporphytria state (temporary drug-induced cutaneous porphyria).

Most toxicities associated with this therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. The local adverse reactions are characteristic of an inflammatory response induced by the photodynamic effect.

Esophageal Carcinoma

The following adverse events were reported over the entire follow-up period in at least 5% of patients treated with PHOTOFRIN® PDT, who had completely or partially obstructing esophageal cancer. Table 5 presents data from 88 patients who received the currently marketed formulation. The relationship of many of these adverse events to PDT with PHOTOFRIN® is uncertain.

TABLE 5. Adverse Events Reported in 5% or More of Patients [a] with Obstructing Esophageal Cancer

BODY SYSTEM/ Adverse Event	Number (%) of Patients n=88	
Patients with at Least One Adverse Event	84	(95%)
AUTONOMIC NERVOUS SYSTEM		
Hypertension	5	(6%)
Hypotension	6	(7%)
BODY AS A WHOLE		
Asthenia	5	(6%)
Back pain	10	(11%)
Chest pain	19	(22%)
Chest pain (substernal)	4	(5%)
Edema generalized	4	(5%)
Edema peripheral	6	(7%)
Fever	27	(31%)
Pain	19	(22%)
Surgical complication	4	(5%)
CARDIOVASCULAR		
Cardiac failure	6	(7%)
GASTROINTESTINAL		
Abdominal pain	18	(20%)
Constipation	21	(24%)
Diarrhea	4	(5%)
Dyspepsia	5	(6%)
Dysphagia	9	(10%)
Eructation	4	(5%)
Esophageal edema	7	(8%)
Esophageal tumor bleeding	7	(8%)
Esophageal stricture	5	(6%)
Esophagitis	4	(5%)

Hematemesis	7	(8%)
Melena	4	(5%)
Nausea	21	(24%)
Vomiting	15	(17%)
HEART RATE/RHYTHM		
Atrial fibrillation	9	(10%)
Tachycardia	5	(6%)
METABOLIC & NUTRITIONAL		
Dehydration	6	(7%)
Weight decrease	8	(9%)
PSYCHIATRIC		
Anorexia	7	(8%)
Anxiety	6	(7%)
Confusion	7	(8%)
Insomnia	12	(14%)
RED BLOOD CELL		
Anemia	28	(32%)
RESISTANCE MECHANISM		
Moniliasis	8	(9%)
RESPIRATORY		
Coughing	6	(7%)
Dyspnea	18	(20%)
Pharyngitis	10	(11%)
Pleural effusion	28	(32%)
Pneumonia	16	(18%)
Respiratory insufficiency	9	(10%)
Tracheoesophageal fistula	5	(6%)
SKIN & APPENDAGES		
Photosensitivity reaction	17	(19%)
URINARY		
Urinary tract infection	6	(7%)

[a] Based on adverse events reported at any time during the entire period of follow-up.

Location of the tumor was a prognostic factor for three adverse events: upper-third of the esophagus (esophageal edema), middle-third (atrial fibrillation), and lower-third, the most vascular region (anemia). Also, patients with large tumors (>10 cm) were more likely to experience anemia. Two of 17 patients with complete esophageal obstruction from tumor experienced esophageal perforations which were considered to be possibly treatment associated; these perforations occurred during subsequent endoscopies.

Serious and other notable adverse events observed in less than 5% of PDT-treated patients with obstructing esophageal cancer in the clinical studies include the following; their relationship to therapy is uncertain. In the gastrointestinal system, esophageal perforation, gastric ulcer, ileus, jaundice, and peritonitis have occurred. Sepsis has been reported occasionally. Cardiovascular events have included angina pectoris, bradycardia, myocardial infarction, sick sinus syndrome, and supraventricular tachycardia. Respiratory events of bronchitis, bronchospasm, laryngotracheal edema, pneumonitis, pulmonary hemorrhage, pulmonary edema, respiratory failure, and stridor have occurred. The temporal relationship of some gastrointestinal, cardiovascular and respiratory events to the administration of light was suggestive of mediastinal inflammation in some patients. Vision-related events of abnormal vision, diplopia, eye pain and photophobia have been reported.

Obstructing Endobronchial Cancer

Table 6 presents adverse events that were reported over the entire follow-up period in at least 5% of patients with obstructing endobronchial cancers treated with PHOTOFRIN® PDT or Nd:YAG. These data are based on the 86 patients who received the currently marketed formulation. Since it seems likely that most adverse events caused by these acute acting therapies would occur within 30 days of treatment, Table 6 presents those events occurring within 30 days of treatment procedure, as well as those occurring over the entire follow-up period. It should be noted that follow-up was 33% longer for the PDT group than for the Nd:YAG group, thereby introducing a bias against PDT when adverse event rates are compared for the entire follow-up period. The extent of follow-up in the 30-day period following treatment was comparable between groups (only 9% more for PDT).

TABLE 6. Adverse Events Reported in 5% or More of Patients with Obstructing Endobronchial Cancers

Number (%) of Patients

BODY SYSTEM/ Adverse Event	Within 30 Days of Treatment				Entire Follow-up Period [a]			
	PDT n=86		Nd:YG n=86		PDT n=86		Nd:YAG n=86	
Patients with at Least One Adverse Event	43	(50%)	33	(38%)	62	(72%)	48	(56%)
BODY AS A WHOLE								
Back pain	3	(3%)	1	(1%)	3	(3%)	5	(6%)
Chest pain	6	(7%)	6	(7%)	7	(8%)	8	(9%)
Edema peripheral	3	(3%)	3	(3%)	4	(5%)	3	(3%)
Fever	7	(8%)	7	(8%)	14	(16%)	8	(9%)
Pain	1	(1%)	4	(5%)	4	(5%)	8	(9%)
CENTRAL NERVOUS SYSTEM								
Dysphonia	3	(3%)	2	(2%)	4	(5%)	2	(2%)
GASTROINTESTINAL								
Constipation	4	(5%)	1	(1%)	4	(5%)	2	(2%)
Dyspepsia	1	(1%)	4	(5%)	2	(2%)	5	(6%)
PSYCHIATRIC								
Anxiety	3	(3%)	0	(0%)	5	(6%)	0	(0%)
Insomnia	4	(5%)	2	(2%)	4	(5%)	3	(4%)
RESPIRATORY								
Bronchitis	9	(10%)	2	(2%)	9	(10%)	2	(2%)
Coughing	5	(6%)	8	(9%)	13	(15%)	11	(13%)
Dyspnea	15	(17%)	7	(8%)	26	(30%)	13	(15%)
Hemoptysis	6	(7%)	5	(6%)	14	(16%)	7	(8%)
Pleural effusion	0	(0%)	0	(0%)	4	(5%)	1	(1%)
Pneumonia	5	(6%)	4	(5%)	10	(12%)	5	(6%)
Pneumothorax	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Respiratory insufficiency	0	(0%)	0	(0%)	5	(6%)	1	(1%)
Sputum increased	4	(5%)	5	(6%)	7	(8%)	6	(7%)
SKIN & APPENDAGES								
Photosensitivity reaction	16	(19%)	0	(0%)	18	(21%)	0	(0%)

[a] Follow-up was 33% longer for the PDT group than for the Nd:YAG group, introducing a bias against PDT when adverse events are compared for the entire follow-up period.

Transient inflammatory reactions in PDT-treated patients occur in about 10% of patients and manifest as fever, bronchitis, chest pain and dyspnea. The incidences of bronchitis and dyspnea were higher with PDT than with Nd:YAG. Most cases of bronchitis occurred within 1 week of treatment and all but one were mild or moderate in intensity. The events usually resolved within 10 days with antibiotic therapy. Treatment-related worsening of dyspnea is generally transient and self-limiting. Debridement of the treated area is mandatory to remove exudate and necrotic tissue. Life-threatening respiratory insufficiency likely due to therapy occurred in 3% of PDT-treated patients and 2% of Nd:YAG-treated patients (see WARNINGS AND PRECAUTIONS).

There was a trend toward a higher rate of fatal hemoptysis (FMH) occurring on the PDT arm (10%) versus the Nd:YAG arm (5%), however, the rate of FMH occurring within 30 days of treatment was the same for PDT and Nd:YAG (4% total events, 3% treatment-associated events). Patients who have received radiation therapy have a higher incidence of FMH after treatment with PDT and after other forms of local therapy than patients who have not received radiation therapy, but analyses suggest that this increased risk may be due to associated prognostic factors such as having a centrally located tumor. The incidence of FMH in patients previously treated with radiotherapy was 21% (6/29) in the PDT group and 10% (3/29) in the Nd:YAG group. In patients with no prior radiotherapy, the overall incidence of FMH was less than 1%. Characteristics of patients at high risk for FMH are described in WARNINGS and CONTRAINDICATIONS.

Other serious or notable adverse events were observed in less than 5% of PDT-treated patients with endobronchial cancer; their relationship to therapy is uncertain. In the respiratory system, pulmonary thrombosis, pulmonary embolism and lung abscess have occurred. Cardiac failure, sepsis and possible cerebrovascular accident have also been reported in one patient each.

Superficial Endobronchial Tumors

The following adverse events were reported over the entire follow-up period in at least 5% of patients with superficial tumors (microinvasive or carcinoma in situ) who received the currently marketed formulation.

TABLE 7. Adverse Events Reported in 5% or More of Patients[a] with Superficial Endobronchial Tumors

Adverse Event	Number (%) of Patients n=90	
Patients with at Least One Adverse Event	44	(49%)
Photosensitivity reaction	20	(22%)
Coughing	8	(9%)
Dyspnea	6	(7%)
Edema	16	(18%)
Exudate	20	(22%)
Obstruction	19	(21%)
Stricture	10	(11%)
Ulceration	8	(9%)

[a] Based on adverse events reported at any time during the entire period of follow-up.

In patients with superficial endobronchial tumors, 44 of 90 patients (49%) experienced an adverse event, two-thirds of which were related to the respiratory system. The most common reaction to therapy was a mucositis reaction in one-fifth of the patients which manifested as edema, exudate, and obstruction. The obstruction (mucus plug) is easily removed with suction or forceps. Mucositis can be minimized by avoiding exposure of normal tissue to excessive light (see PRECAUTIONS). Three patients experienced life-threatening dyspnea: one was given a double dose of light, one was treated concurrently in both mainstem bronchi and the other had had prior pneumonectomy and was treated in the sole remaining main airway (see WARNINGS). Stent placement was required in 3% of the patients due to endobronchial stricture. Fatal hemoptysis occurred within 30 days of treatment in one patient with superficial tumors (1%).

Laboratory Abnormalities

In patients with esophageal cancer, PDT with PHOTOFRIN® may result in anemia due to tumor bleeding. No consistent effects were observed for other parameters or in patients with endobronchial carcinoma.

OVERDOSAGE

PHOTOFRIN® Overdose

There is no information on overdosage situations involving PHOTOFRIN®. Higher than recommended drug doses of two 2 mg/kg doses given two days apart (10 patients) and three 2 mg/kg doses given within two weeks (1 patient), were tolerated without notable adverse reactions. Effects of overdosage on the duration of photosensitivity are unknown. Laser treatment should not be given if an overdose of PHOTOFRIN® is

administered. In the event of an overdose, patients should protect their eyes and skin from direct sulight or bright indoor lights for 30 days. At this time, patients should test for residual photosensitivity (see PRECAUTIONS). PHOTOFRIN® is not dialyzable.

Overdose of Laser Light Following PHOTOFRIN® Injection

Light doses of two to three times the recommended dose have been administered to a few patients with superficial endobronchial tumors. One patient experienced life-threatening dyspnea and the others had no notable complications. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

DOSAGE AND ADMINISTRATION

Photodynamic therapy with PHOTOFRIN® is a two-stage process requiring administration of both drug and light. The first stage of PDT is the intravenous injection of PHOTOFRIN® at 2 mg/kg. Illumination with laser light 40-50 hours following injection with PHOTOFRIN® constitutes the second stage of therapy. A second laser light application may be given 96-120 hours after injection, preceded by gentle debridement of residual tumor (see Administration of Laser Light). In clinical studies, debridement via endoscopy was required 2 days after the initial light application. Standard endoscopic techniques are used for light administration and debridement. Practitioners should be fully familiar with the patient's condition and trained in the safe and efficacious treatment of esophageal or endobronchial cancer using photodynamic therapy with PHOTOFRIN® and associated light delivery devices.

Patients may receive a second course of PDT a minimum of 30 days after the initial therapy; up to three courses of PDT (each separated by a minimum of 30 days) can be given. Before each course of treatment, patients with esophageal cancer should be evaluated for the presence of tracheoesophageal or bronchoesophageal fistula (see CONTRAINDICATIONS). In patients with endobronchial lesions who have recently undergone radiotherapy, sufficient time (approximately 4 weeks) should be allowed between the therapies to ensure that the acute inflammation produced by radiotherapy has subsided prior to PDT (see PRECAUTIONS , Use Before or After Radiotherapy). All patients should be evaluated for the possibility that the tumor may be eroding into a major blood vessel (see CONTRAINDICATIONS).

PHOTOFRIN® Administration

PHOTOFRIN® should be administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight. Reconstitute each vial of PHOTOFRIN® with 31.8 mL of either 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), resulting in a final concentration of 2.5 mg/mL. Shake well until dissolved. Do not mix PHOTOFRIN® with other drugs in the same solution. PHOTOFRIN®, reconstituted with 5% Dextrose Injection (USP) or with 0.9% Sodium Chloride Injection (USP), has a pH in the range of 7 to 8. PHOTOFRIN® has been formulated with an overage to deliver the 75 mg labeled quantity. **The reconstituted product should be protected from bright**

light and used immediately. Reconstituted PHOTOFRIN® is an opaque solution, in which detection of particulate matter by visual inspection is extremely difficult. Reconstituted PHOTOFRIN®, however, like all parenteral drug products, should be inspected visually for particular matter and discoloration prior to administration whenever solution and container permit.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, care must be taken to protect the area from light. There is no known benefit from injecting the extravasation site with another substance.

Administration of Laser Light

Initiate 630 nm wavelength laser light delivery to the patient 40-50 hours following injection with PHOTOFRIN®. A second laser light treatment may be given as early as 96 hours or as late as 120 hours after the initial injection with PHOTOFRIN®. No further injection of PHOTOFRIN® should be given for such retreatment with laser light. Before providing a second laser light treatment, the residual tumor should be debrided. Vigorous debridement may cause tumor bleeding. For endobronchial tumors, debridement of necrotic tissue should be discontinued when the volume of bleeding increases, as this may indicate that debridement has gone beyond the zone of the PDT treatment effect.

The laser system must be approved for delivery of a stable power output at a wavelength of 630 ± 3 nm. Light is delivered to the tumor by cylindrical OPTIGUIDE™ fiber optic diffusers passed through the operating channel of an endoscope/bronchoscope. Instructions for use of the fiber optic and the selected laser system should be read carefully before use. OPTIGUIDE™ cylindrical diffusers are available in several lengths. The choice of diffuser tip length depends on the length of the tumor. Diffuser length should be sized to avoid exposure of nonmalignant tissue to light and to prevent overlapping of previously treated malignant tissue.

Photoactivation of PHOTOFRIN® is controlled by the total light dose delivered:

In the treatment of esophageal cancer, a light dose of 300 joules/cm of tumor length should be delivered. The total power output at the fiber tip is set to deliver the appropriate light dose using exposure times of 12 minutes and 30 seconds.

In the treatment of endobronchial cancer, the light dose should be 200 joules/cm of tumor length. The total power output at the fiber tip is set to deliver the appropriate light dose using exposure times of 8 minutes and 20 seconds. For noncircumferential endobronchial tumors that are soft enough to penetrate, interstitial fiber placement is preferred to intraluminal activation, since this method produces better efficacy and results in less exposure of the normal bronchial mucosa to light. It is important to perform a debridement 2 to 3 days after each light administration to minimize the potential for obstruction caused by necrotic debris (see PRECAUTIONS).

Refer to the OPTIGUIDE™ instructions for use for complete instructions concerning the fiber optic diffuser.

HOW SUPPLIED

PHOTOFRIN® (porfimer sodium) for Injection is supplied as a freeze-dried cake or powder as follows:

NDC 0024-1550-01 -- 75 mg vial

PHOTOFRIN® freeze-dried cake or powder should be stored at Controlled Room Temperature 20-25°C (68-77°F) [see USP].

Spills and Disposal

Spills of PHOTOFRIN® should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light; use of rubber gloves and eye protection is recommended. All contaminated materials should be disposed of in a polyethylene bag in a manner consistent with local regulations.

Accidental Exposure

PHOTOFRIN® is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, PHOTOFRIN® might be an eye and/or skin irritant in the presence of bright light. It is important to avoid contact with the eyes and skin during preparation and/or administration. As with therapeutic overdosage, any overexposed person must be protected from bright light.

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